REMARKS

Claims 1-30 are pending. Claims 3-10 and 15-22 are withdrawn. Claims 1, 2, 11-14 and 23-30 are rejected.

Applicants thank the Examiner for the courtesy of an interview on January 29, 2003 with applicants' undersigned representative. Applicants believe that this Amendment, including Amendments to the Claims, Remarks, and the Declaration of Dr. Rajagopalan, addresses each of the Examiner's basis of rejections and incorporates the Examiner's suggested revisions as discussed during the interview.

Applicants have retained the Examiner's paragraph number designations for convenience.

4.-7. Applicants have corrected the Specification, Abstract, Title, and Claim to Priority as requested by the Examiner.

Applicants respectfully request reconsideration of the Examiner's rejections for the following reasons.

CLAIM REJECTIONS UNDER 35 U.S.C. § 112

Claims 1, 2, 11-14, and 23-30 are rejected under 35 U.S.C. § 112 ¶ 2 as indefinite.

8. Applicants respectfully disagree that the claims are indefinite but have amended all the claims to clarify that the composition comprises a pharmaceutically acceptable carrier and sulfenates having the recited structure.

9.-13. Applicants respectfully disagree that the claims are indefinite and also submit a Declaration by Dr. Rajagopalan, one of the inventors, in further support. Briefly, applicants claim a composition having the recited structure which may bind to a cell via an epitope (E). Applicants do not claim the structure of the binding site between the compound and the target. Applicants also do not claim E for other than the recited targets. Thus, E includes compounds that direct the recited structure to the recited target site; applicants' disclosure provides representative examples.

More particularly, and as further explained in the Declaration, applicants' claimed structure may be targeted to a binding site on a cell using external attachment of an epitope (page 12, lines 17-18; page 14, line 21 to page 15, line 2). E may be hydrogen, or it may be a region of a molecule that specifically binds to a target site on a cell (page 12, lines 17-18). E may be, for example, an antibody, peptide, peptidomimetic, carbohydrate, glycomimetic, drug, hormone, or nucleic acid that binds to a receptor for somatostatin, heat sensitive bacterioendotoxin, neurotensin, bombesin, cholecystekinin, steroids or carbohydrates (page 8, lines 17-20; page 10, lines 12-14).

14. Applicants have amended claims 1, 2, 12, and 14 as suggested by the Examiner to overcome the rejection.

15. Applicants have amended the claims to define "cyanines", but respectfully disagree with the Examiner's rejection and assert that one skilled in the art, based upon the specification, would know that "cyanines" is used in the general sense, that is, to

encompass the group of compounds commonly referred to as cyanines, and not one particular compound.

The attached Declaration provides further support. One example is the recitation at page 7, lines 18-19 that "DYE is an aromatic or a heteroaromatic radical derived from the group consisting of cyanines, ..." These refer to the family of compounds, not one specific compound. Another example is a citation from a text in this field of chemistry confirming applicants' broad definition that "According to general usage, the term "cyanine" designates any cationic dye in which two nuclei of different or same nature are linked by a mono or polymethine chain" (H. Larive and R. Dennilauler, "Cyanine Dyes Derived from Thiazolium Salts" in Thiazole and its Derivatives, J.V. Metzger, Ed.; pp. 23-30; John Wiley & Sons, New York, 1979). Still another example is the quinoline heterocycle cited by the Examiner; this is only one example of the family of cyanine dyes, which include carbocyanine, indocyanine, etc. Hence, quinolines, indocyanines, phthalocyanines, etc. are examples from the family of cyanine dyes. Yet another example is a chemical dictionary's definition of cyanine dye: "One of a series of dyes consisting of two heterocyclic groups (usually quinoline nuclei) connected by a chain of conjugated double bonds containing an odd number of carbon atoms. Example: cyanine blue $C_2H_5NC_9H_6$:$CHC_9H_6NC_2H_5$. They include the isocyanines, merocyanines, cryptocyanines, and dicyanines.

16. Applicants respectfully disagree that claim 1 is not enabled for E binding molecules. The standard for enablement is whether a person skilled in the art would be enabled to practice the invention commensurate in scope with the claims. A patent is

enabling when the disclosures made in the patent application are sufficient to allow a person skilled in the art to make and use the claimed invention. *Spectra-Physics, Inc. v. Coherent, Inc.*, 3 U.S.P.Q.2d 1737 (Fed. Cir.), *cert. denied*, 108 S.Ct. 346 (1987). To determine whether the disclosure is enabling, a two-part analysis is employed: delimiting the scope of the claimed invention *DeGeorge v. Bernier*, 226 U.S.P.Q. 758 (Fed. Cir. 1985), then looking to the disclosures to ascertain whether, given that level of disclosure, a person skilled in the art could successfully reproduce the claimed invention in its entire scope. *De George* at 763.

As further analyzed in the Declaration included as part of this Amendment, and as supported at least at page 12, line 17 to page 14, line 9, applicants claim phototherapuetic agents, specifically, a dye-sulfenate. These agents may be targeted to a particular site in the body, using the portion of the chemical structure designated as E.

Mindful of the Examiner's request to provide structures for E, applicants respectfully assert that one skilled in the art knows these structures based upon applicants' description. For example, when using the composition for dual phototherapy of a prostate tumor, the chemical structure may contain a steroid hormone because prostate tumors are known to contain receptors for steroid hormones. One skilled in the art knows that steroid hormones are compounds containing the cyclopentanoperhydrophenanthrene ring, including but not limited to the following: sterols such as cholesterol, bile acids such as cholanic acid, sex hormones such as estrogens and androgens, adrenocortical hormones such as corticosteroids, cardiac glycosides such as digitoxigenin, sapogenins such as tigogenin, and alkaloids such as

solasodine. Tietz (Ed.), Fundamentals of Clinical Chemistry, Third Edition, p. 554, 1987, W.B. Saunders Co., Philadelphia. Thus, the structure containing any of the above steroid hormone would bind to a cell that has a receptor for a steroid hormone. Selection of the particular steroid hormone is within the level of one skilled in the art; for example, an androgen for a prostate tumor.

Applicant respectfully asserts that one skilled in the art would know the identity of such compounds and would not require an exhaustive list of each and every compound that fits into each of applicants' claimed scope of E. For example, one skilled in the art knows that corticosteroids alone include its synthethic precursors of pregnenolone, progesterone, 17-hydroxypregnenolone, 17-hydroxprogesterone, 11-desoxycorticosterone, cortisol, corticosterone, aldosterone, cortisone, estrone, estraciol, androstenedione, testosterone, etiocholanolone, dehydroepandrosterone, as only a partial list.

Also as explained in the accompanying Declaration, the composition of E will necessarily vary depending upon the site in the body which is to be treated by dual phototherapy ("The novel compounds of the present invention may vary widely depending on the contemplated application"; page 15, lines 22-23). In other words, E is used to locate the compound to the site requiring therapy. Applicants have provided examples of specific biomolecules that will locate the compound at a particular site (supported at least at page 12, line 23 to page 13, line 9). Applicants have provided examples of non-receptor targeting compounds (supported at least at page 13, lines 5 to 12). Applicants have incorporated by reference methods by which antibodies and

peptides are used to target fluorescent dyes to tumors (supported at least at page 13, line 19 to page 7).

Thus, applicants have disclosed how E is to be selected (by determining the lesion requiring treatment). Applicants have disclosed the composition of E (by determining if the site contains a specific receptor binding site such as a prostate tumor, an antigenic binding site such as carcinoembryonic antigen, an atherosclerotic plaque binding site such as a blood vessel). Applicants have disclosed how to conjugate E (references disclosing *Radioactive Labeling of Antibody: A simple and efficient method; Photoimmunodiagnosis with antibody-fluorescein conjugates: in vitro and in vivo preclinical studies;* synthesis and linkage of fluorogenic molecules in U.S. Patent No. 5,714,342; *Novel receptor-targeted fluorescent contrast agents for in vivo tumor imaging*; *Tumor labeling in vivo using cyanine-conjugated monoclonal antibodies; New contrast agents for optical imaging: acid-cleavable conjugates of cyanine dyes with biomolecules*.

Applicants note the Examiner's characterization that the artisan using this invention would be a medicinal chemist Ph.D. in chemistry with several years experience making bioconjugates. Applying the Examiner's characterization on its face and without agreeing or disagreeing, applicants respectfully assert that, based upon the disclosure provided, such an artisan would know which E to select, how to obtain and/or prepare it, and how to attach it to the dye-sulfenate. These disclosures show that applicants fully enabled the artisan as defined by the Examiner to practice the full scope of the claimed composition and method.

Applicants, however, respectfully disagree with the Examiner's assertion that the specification does not enable the invention because there is no procedure give to determine the affinity of any substance to the claimed receptors. Applicants do not claim binding of the inventive compounds to a particular receptor with a particular affinity. Further, characterization of binding affinity is known by one skilled in the art.

Applicants also respectfully disagree with the Examiner's assertion that the predictability in the art of preparing antibodies is low. Antibodies are by nature specific; one skilled in the art uses this specificity to characterize an antigen by preparing an antibody by routine methods, screening, and selection.

Applicants respectfully assert that these remarks have fully overcome this rejection. However, should the Examiner disagree, applicants request the opportunity to supplement this response with detailed citations.

17. Applicants respectfully disagree that the claims lack an adequate written description for the meaning of somatostatin binding molecule, carbohydrate binding molecule, etc.

Adequacy of the written description is a factual consideration, depending upon the nature of invention and the amount of knowledge imparted to one skilled in the art by the disclosure. *In re Wertheim,* 191 U.S.P.Q. 90 (C.C.P.A. 1976).

The Examiner rejects the claims because, as he states, applicants have disclosed no species and have made no assertion that there is any correlation between the function and structure of E.

Applicants refer to their previous analysis at section 16, the accompanying Declaration, and the Examiner's interview summary that a cure of indefiniteness will simultaneously cure a written description rejection.

18. Applicants respectfully disagree that the term "cyanine" in claims 1, 2, 11-14, 23-30 is subject matter not described to reasonably convey the inventors had possession of the invention. As analyzed with reference to paragraph 15, applicants assert that the Examiner's inquiry concerning "the skilled medicinal chemist" would know the inventors had possession of the claimed cyanine dyes. Additional support is provided in the accompanying Declaration.

19. Applicants respectfully disagree that the claims directed to a phototherapeuticprocedure are not enabled for treating target tissue.

As applicants have explained, any tissue to which the compound may be applied, directed, or otherwise located, may be treated by dual phototherapy using the inventive compound and is a target tissue. A target tissue is one requiring phototherapy; it may be a tumor or another type of lesion (page 10, lines 4-5).

Without comment as to the Examiner's characterization of the skilled artisan, applicants' numerous examples provide sufficient enablement to enable one skilled in the relevant art to determine and treat a target tissue. Applicants have provided representative examples of diseases (breast lesions, prostate lesions, atherosclerotic plaques, brain lesions, etc.). Applicants have provided representative examples of targets (organs, tissues, cells). Applicants' method administers the

compound to the target tissue, then exposes the target tissue to light of the disclosed wavelength.

CONCLUSION

For the foregoing reasons, applicants submit that all the rejections have been overcome and that the application is in condition for allowance.

Applicants respectfully petition for a one month extension of time to respond and have submitted a check for this extension. Should any additional fees or surcharges be deemed necessary, the Examiner is authorized to charge fees or credit any overpayment to Deposit Account No. 23-3000.

The Examiner is invited to telephone applicants' undersigned representative if there are any questions.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION

Amend the Title as follows:

[DYE]CYANINE-SULFENATES FOR DUAL PHOTOTHERAPY

CROSS-REFERENCE TO RELATED APPLICATIONS

The Cross-Reference to Related Applications has been amended as follows:

This application is a continuation-in-part of [pending U.S. Application Serial No. 09/484,322, titled Dendrimer Precursor dyes for Imaging, filed on January 18, 2000,] U.S. Patent No. 6,395,257, having the same inventors and assignee as the present invention, said application incorporated herein by reference in its entirety.

Amend the paragraph beginning at page 2, line 10, as follows:

Phototherapy has been in existence for many centuries and has been used to treat various skin surface ailments. As early as 1400 B.C. in India, plant extracts (psoralens), in combination with sunlight, were used to treat vitiligo. In 1903, Von Tappeiner and Jesionek[,] used eosin as a photosensitizer for treating skin cancer, lupus of the skin, and condylomata of female genitalia. Over the years, the combination of psoralens and ultraviolet A (low-energy) radiation has been used to treat a wide variety of dermatological diseases and manifestations including psoriasis,

parapsoriasis, cutaneous T-cell lymphoma, eczema, vitiligo, areata, and neonatal bilirubinemia. Although the potential of cancer phototherapy has been recognized since the early 1900's, systematic studies to demonstrate safety and efficacy began only in 1967 with the treatment of breast carcinoma. In 1975, Dougherty et al. conclusively established that long-term cure is possible with photodynamic therapy (PDT). Currently, phototherapeutic methods are also being investigated for the treatment of some cardiovascular disorders such as atherosclerosis and vascular restenosis, for the treatment of rheumatoid arthritis, and for the treatment of some inflammatory diseases such as Chron's disease.

Amend the paragraph beginning at page 3, line 19, as follows:

Photosensitizers operate via two distinct mechanisms, termed Types 1 and 2. The type 1 mechanism is shown in the following scheme:

$$\text{SENSITIZER} \xrightarrow{h\nu} (\text{SENSITIZER})^*$$

$$(\text{SENSITIZER})^* + \text{TISSUE} \rightarrow \text{TISSUE DAMAGE}$$

Type 1 mechanisms involve direct energy or electron transfer from the photosensitizer to the cellular components thereby causing cell death. Type 2 mechanisms involve two distinct steps, as shown in the following scheme:

$$\text{SENSITIZER} \xrightarrow{h\nu} (\text{SENSITIZER})^*$$

$$(\text{SENSITIZER})^* + {}^3O_2 \text{ (Triplet Oxygen)} \rightarrow {}^1O_2 \text{ (Singlet Oxygen)}$$

$${}^1O_2 \text{ (Singlet Oxygen)} + \text{TISSUE} \rightarrow \text{TISSUE DAMAGE}$$

In the first step, singlet oxygen is generated by energy transfer from the triplet excited state of the photosensitizer to the oxygen molecules surrounding the tissues. In the second step, collision of singlet oxygen with the tissues promotes tissue damage. In both Type 1 and Type 2 mechanisms, the photoreaction proceeds via the lowest triplet state of the sensitizer. Hence, a relatively long triplet lifetime is required for effective phototherapy. In contrast, a relatively short triplet lifetime is required for diagnostic imaging to avoid photodamage to the tissue caused by photosensitizers.

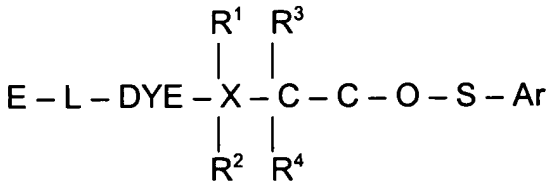
Amend the paragraph beginning at page 6, line 23, as follows:

Thus, there is a need to develop effective phototherapeutic agents that operate via the Type 1 mechanism. Phototherapeutic efficacy can be further enhanced if the excited state photosensitizers can generate reactive intermediates such as free radicals, nitrenes, carbenes, and the like, which have much longer lifetimes than the excited chromophore and have been shown to cause considerable cell injury. Thus, there is a need in the art to develop effective phototherapeutic agents. Phototherapeutic efficacy can be substantially improved if both Type 1 and Type 2 units are integrated into a single compound. This can be accomplished using three types of [formulation] formulations: (a) homogeneous mixtures of Type 1 or Type 2 agents alone, (b) heterogeneous mixtures of Type 1 and Type 2 agents, or (c) a single molecular entity containing both Type 1 and Type 2 functionalities.

IN THE CLAIMS

Claims 1, 2, 12, and 14 have been amended as follows:

1. (AMENDED) A [compound] composition comprising a pharmaceutically acceptable carrier and sulfenates having the formula[,]



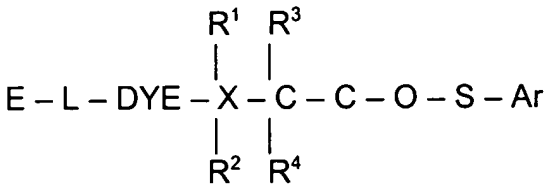
wherein E is selected from the group consisting of somatostatin receptor binding molecules, heat sensitive bacterioendotoxin receptor binding molecules, neurotensin receptor binding molecules, bombesin receptor binding molecules, cholecystekinin receptor binding molecules, steroid receptor binding molecules, and carbohydrate receptor binding molecules, and dihydoxyindolecarboxylic acid; L and X are independently selected from the group consisting of -(R^5)NOC-, -(R^5)NOCCH$_2$O-, -(R^5)NOCCH$_2$CH$_2$O-, -OCN(R^5)-, -HNC(=S)NH-, and HNC(=O)NH-; DYE is an aromatic or a heteroaromatic radical [derived from the group consisting] of cyanines which are conjugated azamethine polyene systems containing a cationic nitrogen atom at one end and a neutral, tertiary nitrogen at the other end, indocyanines, phthalocyanines, rhodamines, phenoxazines, phenothiazines, phenoselenazines, fluoresceins, porphyrins, benzoporphyrins, squaraines, corrins, croconiums, azo dyes, methine dyes, indolenium dyes, crellins, [and] or hypocrellins; R^1 to R^5 are independently selected from the group comprising hydrogen, C1-C10 alkyl, C5-C10 aryl, C1-C10 polyhydroxyalkyl, and C1-C10 polyalkoxyalkyl; and Ar is an aromatic or heteroaromatic

radical [derived from the group consisting] of benzenes, naphthalenes, naphthoquinones, diphenylmethanes, fluorenes, anthracenes, anthraquinones, phenanthrenes, tetracenes, naphthacenediones, pyridines, quinolines, isoquinolines, indoles, isoindoles, pyrroles, imidiazoles, oxazoles, thiazoles, pyrazoles, pyrazines, purines, benzimidazoles, furans, benzofurans, dibenzofurans, carbazoles, acridines, acridones, phenanthridines, thiophenes, benzothiophenes, dibenzothiophenes, xanthenes, xanthones, flavones, coumarins, [and] or anthacylines.

2. (AMENDED) The compound of claim 1 wherein E is selected from the group consisting of somatostatin receptor binding molecules, heat sensitive bacterioendotoxin receptor binding molecules, neurotensin receptor binding molecules, bombesin receptor binding molecules, cholecystekinin receptor binding molecules, and steroid receptor binding molecules; L and X are independently selected from the group consisting of -(R^5)NOC-, and -(R^5)NOCCH_2O -; DYE is [derived from cyanines] a cyanine; R^1 to R^5 are independently selected from the group consisting of hydrogen, C1-C10 alkyl, C5-C10 aryl, and C1-C10 polyhydroxyalkyl; and Ar is an aromatic benzene radical [derived from benzene].

12. (AMENDED) A method of performing a phototherapeutic procedure which comprises the steps of:

(a) administering to a target tissue in an animal [in] an effective amount of sulfenate photosensitizers in a pharmaceutically acceptable carrier, the sulfenates having the formula



wherein E is selected from the group consisting of somatostatin receptor binding molecules, heat sensitive bacterioendotoxin receptor binding molecules, neurotensin receptor binding molecules, bombesin receptor binding molecules, cholecystekinin receptor binding molecules, steroid receptor binding molecules, and carbohydrate receptor binding molecules, and dihydoxyindolecarboxylic acid; L and X are independently selected from the group consisting of -(R^5)NOC-, -(R^5)NOCCH_2O-, -(R^5)NOCCH_2CH_2O-, -OCN(R^5)-, -HNC(=S)NH-, and HNC(=O)NH-; DYE is an aromatic or a heteroaromatic radical [derived from the group consisting] of cyanines which are conjugated azamethine polyene systems containing a cationic nitrogen atom at one end and a neutral, tertiary nitrogen at the other end, indocyanines, phthalocyanines, rhodamines, phenoxazines, phenothiazines, phenoselenazines, fluoresceins, porphyrins, benzoporphyrins, squaraines, corrins, croconiums, azo dyes, methine dyes, indolenium dyes, crellins, [and] or hypocrellins; R^1 to R^5 are independently selected from the group comprising hydrogen, C1-C10 alkyl, C5-C10 aryl, C1-C10 polyhydroxyalkyl, and C1-C10 polyalkoxyalkyl; and Ar is an aromatic or heteroaromatic radical [derived from the group consisting] of benzenes, naphthalenes, naphthoquinones, diphenylmethanes, fluorenes, anthracenes, anthraquinones, phenanthrenes, tetracenes, naphthacenediones, pyridines, quinolines, isoquinolines, indoles, isoindoles, pyrroles, imidiazoles, oxazoles, thiazoles, pyrazoles, pyrazines,

purines, benzimidazoles, furans, benzofurans, dibenzofurans, carbazoles, acridines, acridones, phenanthridines, thiophenes, benzothiophenes, dibenzothiophenes, xanthenes, xanthones, flavones, coumarins, [and] or anthacylines; and

(b) exposing said target tissues with the light of wavelength between 300 and 950 nm with sufficient power and fluence rate to cause necrosis or apoptosis of the said target tissue.

14. (AMENDED) The method of claim 12, wherein E is selected from the group consisting of somatostatin receptor binding molecules, heat sensitive bacterioendotoxin receptor binding molecules, neurotensin receptor binding molecules, bombesin receptor binding molecules, cholecystekinin receptor binding molecules, and steroid receptor binding molecules; L and X are independently selected from the group consisting of -(R^5)NOC-, and -(R^5)NOCCH_2O -; DYE is [derived from cyanines] a cyanine; R^1 to R^5 are independently selected from the group consisting of hydrogen, C1-C10 alkyl, C5-C10 aryl, and C1-C10 polyhydroxyalkyl; and Ar is an aromatic benzene radical [derived from benzene].

ABSTRACT

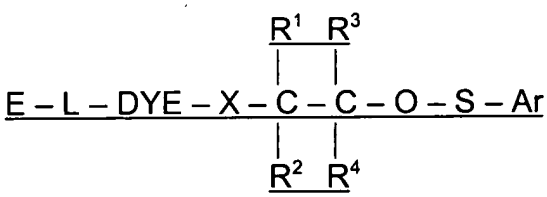
The Abstract has been amended as follows:

[DYE]CYANINE-SULFENATES FOR DUAL PHOTOTHERAPY

ABSTRACT

[The present invention discloses dye-sulfenate derivatives and their bioconjugates for dual phototherapy of tumors and other lesions. The compounds of the present invention may contain either a mixture of Type 1 and Type 2 agents or a single entity that integrates both units in the same molecules.]

Dye-sulfenate derivatives and their bioconjugates for dual phototherapy of tumors and other lesions. The compounds comprise sulfenates having the formula,



where E is selected from the group consisting of somatostatin receptor binding molecules, heat sensitive bacterioendotoxin receptor binding molecules, neurotensin receptor binding molecules, bombesin receptor binding molecules, cholecystekinin receptor binding molecules, steroid receptor binding molecules, and carbohydrate receptor binding molecules, and dihydoxyindolecarboxylic acid; L and X are independently selected from the group consisting of $-(R^5)NOC-$, $-(R^5)NOCCH_2O-$, $-(R^5)NOCCH_2CH_2O-$, $-OCN(R^5)-$, -HNC(=S)NH-, and HNC(=O)NH-; DYE is an aromatic or a heteroaromatic radical derived from the group consisting of cyanines, indocyanines, phthalocyanines, rhodamines, phenoxazines, phenothiazines,

phenoselenazines, fluoresceins, porphyrins, benzoporphyrins, squaraines, corrins, croconiums, azo dyes, methine dyes, indolenium dyes, crellins, and hypocrellins; R^1 to R^5 are independently selected from the group comprising hydrogen, C1-C10 alkyl, C5-C10 aryl, C1-C10 polyhydroxyalkyl, and C1-C10 polyalkoxyalkyl; and Ar is an aromatic or heteroaromatic radical derived from the group consisting of benzenes, naphthalenes, naphthoquinones, diphenylmethanes, fluorenes, anthracenes, anthraquinones, phenanthrenes, tetracenes, naphthacenediones, pyridines, quinolines, isoquinolines, indoles, isoindoles, pyrroles, imidiazoles, oxazoles, thiazoles, pyrazoles, pyrazines, purines, benzimidazoles, furans, benzofurans, dibenzofurans, carbazoles, acridines, acridones, phenanthridines, thiophenes, benzothiophenes, dibenzothiophenes, xanthenes, xanthones, flavones, coumarins, and anthacylines. The compounds are designed to produce both Type 1 and Type 2 phototherapeutic [effect] effects at once using a dual wavelength light source that will produce singlet oxygen and free radicals at the lesion of interest.